REMARKS

Responsive to the preliminary lack of unity determination, applicants provisionally elect group IX, 1-4, 7-9, 11-15, 19, 20, 22 and 23, drawn to a transgenic nonhuman animal expressing at least one transgene comprising a DNA sequence encoding all APP-Arctic mutation and another APP mutation associated with Alzheimer's disease, wherein the endogenous APP is expressive, and the corresponding methods, with traverse.

The reasons for traverse follow:

Claim 1 relates to a transgenic non-human animal expressing at least one transgene comprising a DNA sequence encoding a heterologous APP comprising at least the mutation E693G and a further Alzheimer's disease (AD) pathogenic mutation or a further transgene affecting AD pathogenesis resulting in an increase of soluble Aβ-aggregates.

The Official Action alleges that the inventions listed as groups I-XII do not relate to a single general inventive concept under PCT Rule 13.1 because any same or corresponding special technical features were already disclosed by Chishti et al and Nilsberth et al.

However, under PCT Rule 13.2, the application shall be considered to have unity of invention if all inventions have the same or corresponding special technical feature, i.e. technical

feature that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

In the present case, the special technical feature is the provision of the Arctic mutation (E693G) *in combination with* a further mutation affecting AD pathogenesis, and these mutations together result in an increase of intracellular soluble Aβ-aggregates. These combined mutations give a synergistic effect in that the Arctic mutation enhances the formation of intracellular soluble Aβ-aggregates from Aβ monomers. The further mutation may be a mutation increasing production of Aβ peptides or decreasing the clearance of Aβ peptides. Together, they increase the total amount of intracellular soluble aggregates in the brain of the transgenic animal more than each mutation would on its own, which in turn leads to an animal model that is very effective for studying human Alzheimer's disease.

The above technical feature, i.e., the combination of the Arctic mutation with another mutation resulting in an increase of intracellular soluble Aβ-aggregates, is not disclosed in the prior art.

In this regard, Applicants note the following:

The Arctic mutation (E693) was the first APP mutation located inside A that was proven to cause Alzheimer's disease. Since the Arctic mutation is located *inside* Aβ, the amino acid sequence of Aβ is changed. Thus, variants of the Aβ molecules with altered biochemical properties are produced.

In contrast, the Indiana mutation (V717F), used by Chishti et al., is *outside* of Aβ, and *normal Aβ molecules are produced*. The Indiana mutation leads to an increased amount of the longer pathogenic Aβ42 form being produced.

Thus, the Indiana mutation (V717F) and the Arctic mutation (E693G) lead to Alzheimer's disease by different molecular mechanisms. The Indiana mutation increases levels of the pathogenic Aβ42 form, while the Arctic mutation increases the formation of Aβ protofibrils (i.e., soluble aggregates of Aβ) from Aβ peptides.

The combination of the Swedish (670/671) and Indiana (717) mutations described in Chishti et al., give increased amounts of Aβ (see the abstract), but the transgenic mice do not develop increased amounts of intracellular soluble Aβ aggregates. Furthermore, Chishti et al. do not even mention the Arctic mutation, which is at the very center of the present invention.

As to the article by Nilsberth et al., the article does not teach how to generate intracellular soluble Aβ-aggregates. The experiments described by Nilsberth et al. have been done in a test tube (Fig. 4, page 890). There are no cells and no brains present in this experiment. Furthermore, Nilsberth et al. do not suggest that the Arctic mutation may be combined with any other mutation in a transgenic animal to give a synergistic effect that would lead to a useful animal model, as is the subject matter of the present application.

Thus, the special technical feature required by PCT Rule 13.2 is the provision of the Arctic mutation (E693G) in combination with a further mutation affecting Aβ pathogenesis, which results in an increase of intracellular soluble Aβ-aggregates. This is neither disclosed by Chishti et al. and by Nilsberth et al. individually, nor suggest by their combination.

Therefore, the requirement for restriction is improper and should be withdrawn.

A favorable action on the merits of all the claims, in their full scope, is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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